L Number	Hits	Search Text	DB	Time stamp
1	6	(neurit$2 or neurocy$3) and extract$2 same citrus	USPAT; US-PGPUB; EPO; DERWENT	2002/12/14 19:48
2	59	(neurodegenerat$5 or alzheimer$3 or dementia or ischem$4) and extract$2 same citrus	USPAT; US-PGPUB; EPO; DERWENT	2002/12/14 17:52
3	1	("6451837").PN.	USPAT; US-PGPUB	2002/12/14 19:45
4	0	("20010233768").PN.	USPAT; US-PGPUB	2002/12/14 19:46
5	1	("20010046963").PN.	USPAT; US-PGPUB	2002/12/14 19:47
6	1	("20010047032").PN.	USPAT; US-PGPUB	2002/12/14 19:47

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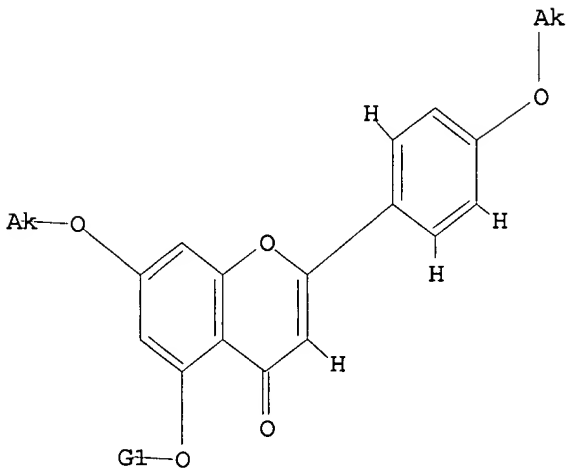
L4 STRUCTURE UPLOADED

=> d l4
L4 HAS NO ANSWERS
L4 STR



H 2

Ak 1

G1 [@1], [@2]

Structure attributes must be viewed using STN Express query preparation.

```
=> s l6 and (neurodegenera? or alzheimer? or dementi? or ischem?)
          1877 L6
         11331 NEURODEGENERA?
         24330 ALZHEIMER?
          7530 DEMENTI?
         57712 ISCHEM?
L7            7 L6 AND (NEURODEGENERA? OR ALZHEIMER? OR DEMENTI? OR ISCHEM?)

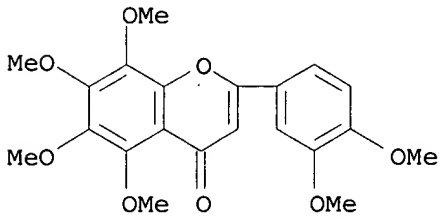
=> d l7 abs ibib kwic hitstr 1-7

L7   ANSWER 1 OF 7  CAPLUS  COPYRIGHT 2002 ACS
AB   Polyalkoxyflavonoids, esp. nobiletin and tangeretin, in the Rutaceae ext.
     are useful for control and relief of neurodegenerative diseases
     such as cerebral ischemia.  Dried peel of Citrus unshiu was
     extd. with ethanol and nobiletin and tangeretin identified in the ext. by
     known method.  Biol. activity of the Citrus unshiu ext. on the PC12 cell
     was shown.
ACCESSION NUMBER:         2002:148735  CAPLUS
DOCUMENT NUMBER:          136:164277
TITLE:                    Neurite outgrowth factor in Rutaceae extract
INVENTOR(S):              Ito, Hisatomi; Tamura, Shinya; Miyazaki, Toshiji
PATENT ASSIGNEE(S):       Nagase and Co., Ltd., Japan
SOURCE:                   Jpn. Kokai Tokkyo Koho, 9 pp.
                          CODEN: JKXXAF
DOCUMENT TYPE:            Patent
LANGUAGE:                 Japanese
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

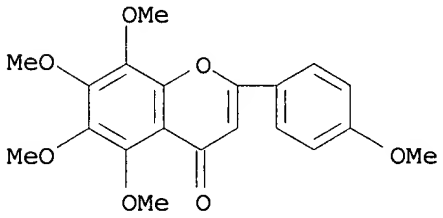
     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  --------       ---------------  --------
     JP 2002060340      A2   20020226       JP 2000-248021   20000817
     US 2002040052      A1   20020404       US 2001-927038   20010809
PRIORITY APPLN. INFO.:                   JP 2000-248021   A  20000817
OTHER SOURCE(S):          MARPAT 136:164277
AB   Polyalkoxyflavonoids, esp. nobiletin and tangeretin, in the Rutaceae ext.
     are useful for control and relief of neurodegenerative diseases
     such as cerebral ischemia.  Dried peel of Citrus unshiu was
     extd. with ethanol and nobiletin and tangeretin identified in the ext. by
     known method..  .  .
ST   Rutaceae ext neurite outgrowth factor neurodegenerative disease;
     polyalkoxyflavonoid neurodegenerative disease control Rutaceae
     ext
IT   Brain, disease
        (ischemia; neurite outgrowth agent)
IT   Alzheimer's disease
     Citrus depressa
     Drugs
     Health food
     Rutaceae
     Satsuma
        (neurite outgrowth agent)
IT   478-01-3P, Nobiletin 481-53-8P, Tangeretin
     RL: PUR (Purification or recovery); THU (Therapeutic use); BIOL
     (Biological study); PREP (Preparation); USES (Uses)
        (neurite outgrowth agent)
IT   478-01-3P, Nobiletin 481-53-8P, Tangeretin
```

RL: PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(neurite outgrowth agent)

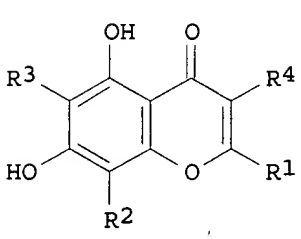
RN 478-01-3 CAPLUS
CN 4H-1-Benzopyran-4-one, 2-(3,4-dimethoxyphenyl)-5,6,7,8-tetramethoxy- (9CI) (CA INDEX NAME)



RN 481-53-8 CAPLUS
CN 4H-1-Benzopyran-4-one, 5,6,7,8-tetramethoxy-2-(4-methoxyphenyl)- (9CI) (CA INDEX NAME)



L7 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2002 ACS
GI



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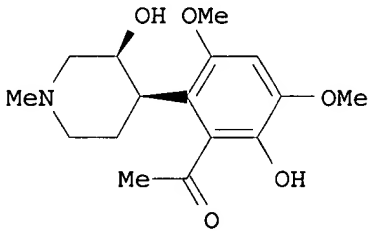


II

AB The invention concerns novel products I [R1 = mono- or bicyclic (un)substituted (un)satd. carbocycle, heterocycle; R2, R3 one = H and the other = (un)substituted piperidinyl; R4 = H, alkyl, (un)substituted Ph] in all isomeric and salt forms for used as medicinals. Thus, the trifluoracetate of I [R1 = C6H4Cl-2-F-4, R2 = 3-hydroxy-1-methyl-4-piperidinyl-(3S,4R), R3 = R4 = H] was prepd. via the condensation of piperidine deriv. II with Me 2-chloro-4-fluorobenzoate, cyclization with aq. HCl, O-demethylation with Reillex pyridine TM 402 hydroiodide and trifluoroacetate salt formation. Pharmaceutical compns. contg. I can be

used as antimitotics, for cancer chemotherapy, for treatment of psoriasis, as parasiticides or for treatment of **Alzheimer**'s disease.

ACCESSION NUMBER: 2001:661419 CAPLUS
DOCUMENT NUMBER: 135:226823
TITLE: Preparation of flavone derivatives for use as medicines
INVENTOR(S): Haesslein, Jean-luc; Lefrancois, Dominique; Uridat, Eric; Zhang, Jidong
PATENT ASSIGNEE(S): Aventis Pharma S.A., Fr.
SOURCE: PCT Int. Appl., 87 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001064673	A1	20010907	WO 2001-FR561	20010227
W: AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
FR 2805538	A1	20010831	FR 2000-2528	20000229
EP 1261603	A1	20021204	EP 2001-909906	20010227
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: FR 2000-2528 A 20000229
WO 2001-FR561 W 20010227
OTHER SOURCE(S): CASREACT 135:226823; MARPAT 135:226823

AB . . . contg. I can be used as antimitotics, for cancer chemotherapy, for treatment of psoriasis, as parasiticides or for treatment of **Alzheimer**'s disease.

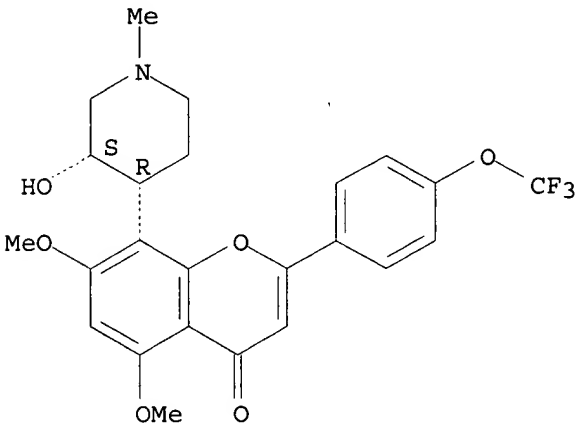
ST . . . medicinal use; antimitotic flavone deriv prepn; cancer chemotherapy flavone deriv prepn; psoriasis medicament flavone deriv prepn; parasiticide flavone deriv prepn; **Alzheimer** disease medicament flavone deriv prepn

IT **Alzheimer**'s disease
Mitosis
Psoriasis
(medicaments; prepn. of flavone derivs. for use as medicines)

IT 9017-40-7DP, Reillex 402, iodohydrate deriv. 18820-83-2P, Pyridine hydroiodide 358739-44-3P 358739-45-4P 358739-46-5P 358739-47-6P
358739-48-7P 358739-49-8P 358739-51-2P 358739-52-3P 358739-53-4P
358739-54-5P 358739-55-6P 358739-56-7P 358739-57-8P 358739-58-9P
358739-59-0P 358739-60-3P 358739-61-4P 358739-62-5P 358739-63-6P
358739-64-7P 358739-65-8P 358739-66-9P 358739-67-0P 358739-69-2P
358739-70-5P 358739-71-6P 358739-72-7P 358739-73-8P 358739-74-9P
358739-75-0P 358739-76-1P 358739-77-2P 358739-78-3P 358739-79-4P
358739-80-7P 358739-81-8P 358739-82-9P **358739-83-0P**
358739-84-1P 358739-85-2P 358739-86-3P 358739-87-4P 358739-88-5P
358739-89-6P 358739-90-9P 358739-91-0P 358979-93-8P 358979-94-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of flavone derivs. for use as medicines)

IT **358739-83-0P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of flavone derivs. for use as medicines)
RN 358739-83-0 CAPLUS
CN 4H-1-Benzopyran-4-one, 8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]-5,7-dimethoxy-2-[4-(trifluoromethoxy)phenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2002 ACS
AB This invention relates to the use of flavone or derivs. thereof for the treatment of diseases mediated by cyclooxygenase-2 or NF.kappa.B. The flavones can be administered in oral dosage forms or foods.
ACCESSION NUMBER: 2001:626002 CAPLUS
DOCUMENT NUMBER: 135:185492
TITLE: Flavones for the treatment of COX-2 and/or NF.kappa.B-mediated diseases
INVENTOR(S): Wenzel, Uwe; Daniel, Hannelore
PATENT ASSIGNEE(S): Basf A. -G., Germany
SOURCE: Jpn. Kokai Tokkyo Koho, 13 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2001233768	A2	20010828	JP 2001-49370	20010223
EP 1127572	A2	20010829	EP 2001-103200	20010212
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 2001046963	A1	20011129	US 2001-782306	20010214
CN 1318371	A	20011024	CN 2001-116513	20010225

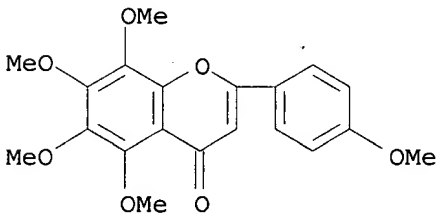
PRIORITY APPLN. INFO.: US 2000-185179P P 20000225
OTHER SOURCE(S): MARPAT 135:185492
IT Adhesion, biological

Analgesics
Anti-**Alzheimer**'s agents
Anti-inflammatory agents
Antiarthritics
Antidiabetic agents
Antipyretics
Antirheumatic agents
Beverages
Breakfast cereal
Milk preparations
Nutrients
(flavones for treatment of COX-2 and/or NF.kappa.B-mediated diseases)

IT **481-53-8**, Tangeretin 486-66-8, Daidzein 487-26-3, Flavanone 491-54-3, Kaempferide 491-67-8, Baicalein 491-70-3, Luteolin 491-80-5, Biochanin 520-26-3, Hesperidin 520-27-4, Diosmin 520-33-2, Hesperetin 525-82-6, Flavone 528-48-3, Fisetin 529-44-2, Myricetin 529-59-9, Genistin 577-85-5, 3-Hydroxyflavone 14259-47-3, Didymin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); FFD (Food or feed use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(flavones for treatment of COX-2 and/or NF.kappa.B-mediated diseases)

IT **481-53-8**, Tangeretin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); FFD (Food or feed use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(flavones for treatment of COX-2 and/or NF.kappa.B-mediated diseases)

RN 481-53-8 CAPLUS
CN 4H-1-Benzopyran-4-one, 5,6,7,8-tetramethoxy-2-(4-methoxyphenyl)- (9CI) (CA INDEX NAME)



L7 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2002 ACS

AB Polyhydroxylated arom. compds., and compns. contg. them, are useful for the treatment of amyloidosis, esp. **Alzheimer**'s disease, and for the treatment of diseases characterized by .alpha.-synuclein fibril formation, esp. Lewy body disease and Parkinson's disease.

ACCESSION NUMBER:	2001:507525 CAPLUS
DOCUMENT NUMBER:	135:102574
TITLE:	Polyhydroxylated aromatic compounds for the treatment of amyloidosis and .alpha.-synuclein fibril diseases
INVENTOR(S):	Castillo, Gerardo M.; Choi, Paula Y.; Snow, Alan D.
PATENT ASSIGNEE(S):	Proteo Tech, Inc., USA
SOURCE:	PCT Int. Appl., 50 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1

09/927,038

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001049281	A2	20010712	WO 2000-US35715	20001228
WO 2001049281	A3	20020510		
W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2001047032	A1	20011129	US 2000-748748	20001226
EP 1244435	A2	20021002	EP 2000-989636	20001228
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: US 1999-173958P P 19991230
US 2000-748748 A 20001226
WO 2000-US35715 W 20001228

OTHER SOURCE(S): MARPAT 135:102574

AB Polyhydroxylated arom. compds., and compns. contg. them, are useful for the treatment of amyloidosis, esp. **Alzheimer**'s disease, and for the treatment of diseases characterized by .alpha.-synuclein fibril formation, esp. Lewy body disease and Parkinson's disease.

ST hydroxyphenol hydroxypyran deriv amyloidosis synuclein **Alzheimer**

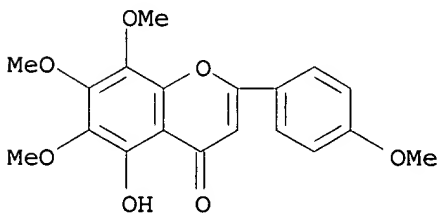
IT **Alzheimer**'s disease
Amyloidosis
Anti-**Alzheimer**'s agents
Antiparkinsonian agents
Down's syndrome
Parkinson's disease
(polyhydroxylated arom. compds. for the treatment of amyloidosis and .alpha.-synuclein fibril diseases)

IT 51-61-6, Dopamine, biological studies 59-92-7, Dopa, biological studies 72-48-0, Alizarin 77-95-2, Quinic acid 81-61-8, Quinalizarin 82-12-2, Rufigallol 82-83-7, Puberulonic acid 83-85-2, Fuscin 87-88-7, Chloranilic acid 90-18-6, Quercetagetin 90-19-7, Rhamnetin 99-11-6, Citrazinic acid 99-23-0, Puberulic acid 117-12-4, Anthrarufin 117-39-5, Quercetin 118-76-3, Rhodizonic acid 121-79-9, Propyl gallate 128-68-7, Phenicin 148-25-4, Chromotropic acid 149-45-1, Tiron 149-91-7, Gallic acid, biological studies 152-84-1, Ruberythric acid 153-18-4, Rutin 154-23-4, catechin 301-19-9, Robinin 305-01-1, Esculetin 319-89-1, Tetroquinone 437-50-3, Gentisin 446-72-0, Genistein 475-25-2, Hematein 475-54-7, Oosporein 478-43-3, Rhein 478-60-4, Citromycetin 480-15-9, Datiscetin 480-16-0, Morin 480-17-1, Leucocyanidin 480-40-0, Chrysin 480-44-4, Acacetin 481-74-3, Chrysophanic acid 484-89-9, Fumigatin 486-35-1, Daphnetin 489-32-7, Icariin 490-46-0, Epicatechin 491-45-2, Phloroglucide 491-50-9, Quercimeritrin 491-58-7, Chrysarobin 491-67-8, Baicalein 491-70-3, Luteolin 497-75-6, Dioxethedrine 499-14-9, Chondrosine 501-15-5, Deoxyepinephrine 517-82-8, Echinochrome a 517-88-4, Alkannin 517-92-0, Chrysamminic acid 518-82-1, Emodin 519-34-6, Maclurin 520-18-3, Kaempferol 520-27-4, Diosmin 520-34-3, Diosmetin 520-36-5, Apigenin 524-30-1, Fraxin 528-21-2, Gallacetophenone 528-48-3,

Fisetin 528-50-7, Cellobiose 528-53-0, Delphinidin 528-58-5, Cyanidin 529-53-3, Scutellarein 531-58-8, Cichoriin 533-73-3, 1,2,4-Benzenetriol 536-08-3, Digallic acid 548-80-1, chromotrope 2B 548-83-4, Galangin 550-24-3, Embelin 552-21-6, Methylenedigallic acid 552-58-9, Eriodictyol 568-02-5, Alizarin blue 568-93-4 569-77-7, Purpurogallin 574-84-5, Fraxetin 577-33-3, Anthrarobin 578-74-5, Apigetrin 602-64-2, Anthragallol 602-92-6, Dibromogallic acid 618-73-5, Gallamide 831-61-8, Ethyl gallate 970-73-0, Gallocatechin 970-74-1, Epigallocatechin 1143-38-0, Anthralin 1260-17-9, Carminic acid 1397-77-9, Actinorhodine 1403-56-1, Fomecin a 1404-52-0, Rhodomycin b 1471-96-1, Echinochrome a 1562-85-2, Gallocyanine 1702-77-8, Fusarubin 1927-04-4, 5-Hydroxydopamine 2103-64-2, Gallein 2611-67-8, Cyanidin 3,5-diglucoside **2798-20-1**, Gardenin b 3101-51-7, Ergoflavin 4589-33-7, Bostrycoidin 5908-63-4, Baptigenin 7084-24-4, Cyanidin 3-glucoside 7085-55-4, Troxerutin 10140-70-2, Curvularin 13405-60-2, .beta. Glucogallin 15979-35-8, Laccaic acid a 16545-11-2, Guamecycline 16790-41-3, Fomecin b 17249-00-2, Laccaic acid b 18376-31-3, Cyanidin 3-sophoroside 18499-84-8, Laccaic acid d 18499-92-8, Kermesic acid 18719-76-1, Cyanidin 3-rhamnoglucoside 19879-06-2, Granaticin 20004-62-0, Resistomycin 20725-03-5, Fustin 20830-81-3, Daunorubicin 21187-73-5, Gardenin a 21637-25-2, Isoquercitrin 23214-92-8, Doxorubicin 23241-56-7, Laccaic acid c 23444-65-7, Alkannin 23651-95-8, Droxidopa 23666-50-4, Rhodomycin a 27267-69-2, Collinomycin 27613-78-1, Alizarinsulfonic acid 28860-95-9, Carbidopa **29202-00-4**, Gardenin d 29550-05-8, Gardenin c 29550-07-0, Gardenin e 35595-03-0, Centaurein 36413-60-2, Quinic acid 38820-68-7, Cyanidin 3-sophoroside 42927-70-8, Apiose 50935-04-1, Carubicin 52479-85-3, Exifone 53318-36-8, .alpha. Glucogallin 67227-56-9, Fenoldopam 71628-96-1, Menogaril 75775-33-6, Purpurin 80455-68-1, Fredericamycin a 97689-87-7, tunichrome B1 349584-11-8
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polyhydroxylated arom. compds. for the treatment of amyloidosis and .alpha.-synuclein fibril diseases)

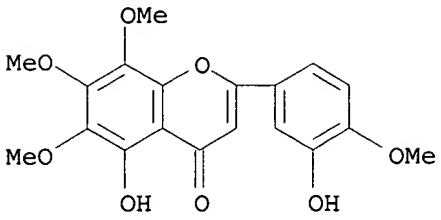
IT **2798-20-1**, Gardenin b **29202-00-4**, Gardenin d
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polyhydroxylated arom. compds. for the treatment of amyloidosis and .alpha.-synuclein fibril diseases)

RN 2798-20-1 CAPLUS
CN 4H-1-Benzopyran-4-one, 5-hydroxy-6,7,8-trimethoxy-2-(4-methoxyphenyl)- (9CI) (CA INDEX NAME)



RN 29202-00-4 CAPLUS
CN 4H-1-Benzopyran-4-one, 5-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-6,7,8-

trimethoxy- (9CI) (CA INDEX NAME)



L7 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2002 ACS

AB Beadlets comprising xanthophylls and carotenes and/or retinoids, dietary supplements comprising these beadlets and methods of use are disclosed.

ACCESSION NUMBER: 2001:208119 CAPLUS
DOCUMENT NUMBER: 134:236643
TITLE: Stable carotene-xanthophyll beadlet compositions and methods of use
INVENTOR(S): Lang, John C.
PATENT ASSIGNEE(S): Alcon Universal Ltd., Switz.
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001019383	A1	20010322	WO 2000-US24439	20000906
W: AU, BR, CA, JP, MX, TR, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1212071	A1	20020612	EP 2000-959942	20000906
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				

PRIORITY APPLN. INFO.: US 1999-397472 A 19990917
WO 2000-US24439 W 20000906

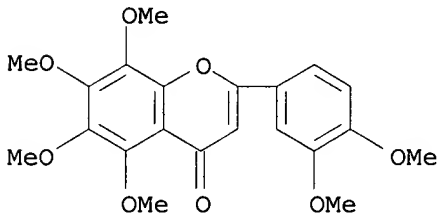
IT Eye, disease
(retina, **ischemia**; stable carotene-xanthophyll beadlet compns. and methods of use)

IT 57-50-1, Sucrose, biological studies 59-30-3, Folic acid, biological studies 59-67-6, Niacin, biological studies 65-23-6, Pyridoxine 68-19-9, Cyanocobalamin 79-83-4, Pantothenic acid 83-88-5, Vitamin B2, biological studies 110-44-1, Sorbic acid 117-39-5, Quercetin 127-40-2, Lutein 137-66-6, Ascorbyl palmitate 144-68-3, Zeaxanthin 153-18-4, Rutin 472-61-7, Astaxanthin 472-70-8, Cryptoxanthin 472-89-9, .epsilon.-Carotene 472-92-4, .delta.-Carotene 472-93-5, .gamma.-Carotene **478-01-3**, Nobiletin 480-18-2 480-40-0, Chrysin 480-44-4, Acacetin **481-53-8**, Tangeretin 502-65-8, .psi.,.psi.-Carotene 514-78-3, Canthaxanthin 520-18-3, Kaempferol 520-36-5, Apigenin 532-32-1, Sodium benzoate 551-15-5, Liquiritin 557-04-0, Magnesium stearate 557-34-6, Zinc acetate 1406-18-4, Vitamin E 3211-76-5, L-Selenomethionine 4345-03-3, .alpha.-Tocopherol succinate 7235-40-7, .beta.-Carotene 7439-96-5, Manganese, biological

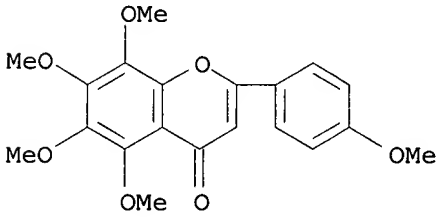
studies 7440-47-3, Chromium, biological studies 7440-50-8, Copper, biological studies 7440-50-8D, Copper, amino acid chelates, biological studies 7488-99-5, .alpha.-Carotene 7631-86-9, Silica, biological studies 7757-93-9, Dicalcium phosphate 7782-49-2, Selenium, biological studies 9004-65-3, Hydroxypropylmethylcellulose 9005-25-8, Starch, biological studies 9005-65-6, Polysorbate 80 13463-67-7, Titanium dioxide, biological studies 25322-68-3, Polyethylene glycol 74811-65-7, Croscarmellose sodium
RL: FFD (Food or feed use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stable carotene-xanthophyll beadlet compns. and methods of use)

IT **478-01-3**, Nobiletin **481-53-8**, Tangeretin
RL: FFD (Food or feed use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stable carotene-xanthophyll beadlet compns. and methods of use)

RN 478-01-3 CAPLUS
CN 4H-1-Benzopyran-4-one, 2-(3,4-dimethoxyphenyl)-5,6,7,8-tetramethoxy- (9CI) (CA INDEX NAME)



RN 481-53-8 CAPLUS
CN 4H-1-Benzopyran-4-one, 5,6,7,8-tetramethoxy-2-(4-methoxyphenyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2002 ACS

AB Various dietary flavonoids were evaluated in vitro for their inhibitory effect on xanthine oxidase, which has been implicated in oxidative injury to tissue by **ischemia**-reperfusion. Xanthine oxidase activity was detd. by directly measuring uric acid formation by HPLC. The structure-activity relationship revealed that the planar flavones and flavonols with a 7-hydroxyl group such as chrysin, luteolin, kaempferol, quercetin, myricetin, and isorhamnetin inhibited xanthine oxidase activity at low concns. (IC50 values from 0.40 to 5.02 .mu.M) in a mixed-type mode, while the nonplanar flavonoids, isoflavones and anthocyanidins were less

inhibitory. These results suggest that certain flavonoids might suppress in vivo the formation of active oxygen species and urate by xanthine oxidase.

ACCESSION NUMBER: 1999:725048 CAPLUS
DOCUMENT NUMBER: 132:44494
TITLE: Inhibition of xanthine oxidase by flavonoids
AUTHOR(S): Nagao, Akihiko; Seki, Michiko; Kobayashi, Hidetaka
CORPORATE SOURCE: National Food Research Institute, Ministry of Agriculture, Forestry and Fisheries, Tsukuba, 305-8642, Japan
SOURCE: Bioscience, Biotechnology, and Biochemistry (1999), 63(10), 1787-1790
CODEN: BBBIEJ; ISSN: 0916-8451
PUBLISHER: Japan Society for Bioscience, Biotechnology, and Agrochemistry
DOCUMENT TYPE: Journal
LANGUAGE: English

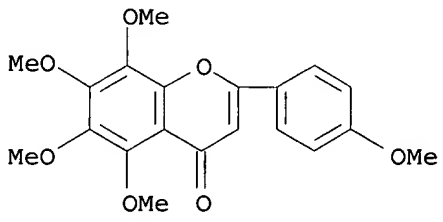
AB . . . evaluated in vitro for their inhibitory effect on xanthine oxidase, which has been implicated in oxidative injury to tissue by **ischemia**-reperfusion. Xanthine oxidase activity was detd. by directly measuring uric acid formation by HPLC. The structure-activity relationship revealed that the planar. . .

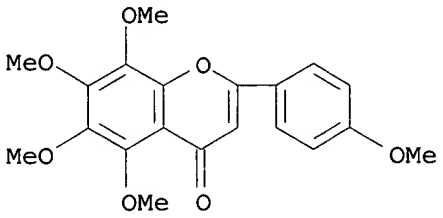
IT Antioxidants
Ischemia
Structure-activity relationship
(structure-related inhibition of xanthine oxidase by flavonoids)

IT 60-82-2, Phloretin 90-19-7, Rhamnetin 117-39-5, Quercetin 134-01-0, Peonidin 134-04-3, Pelargonidin 153-18-4, Rutin 154-23-4, + Catechin 446-72-0, Genistein 480-18-2, Taxifolin 480-19-3, Isorhamnetin 480-40-0, Chrysin **481-53-8**, Tangeretin 486-66-8, Daidzein 487-26-3, Flavanone 490-46-0, -Epicatechin 491-70-3, Luteolin 520-18-3, KAempferol 520-33-2, Hesperitin 525-82-6, Flavone 528-53-0, Delphinidin 528-58-5, Cyanidin 529-44-2, Myricetin 574-12-9, Isoflavone 577-85-5, Flavonol 863-03-6, -Epicatechin gallate 970-74-1, -Epigallocatechin 989-51-5, (-)-Epigallocatechin gallate 1151-98-0, Apigenidin 1481-83-0, 3-Flavanol 1621-55-2 14051-53-7
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(structure-related inhibition of xanthine oxidase by flavonoids)

IT **481-53-8**, Tangeretin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(structure-related inhibition of xanthine oxidase by flavonoids)

RN 481-53-8 CAPLUS
CN 4H-1-Benzopyran-4-one, 5,6,7,8-tetramethoxy-2-(4-methoxyphenyl)- (9CI) (CA INDEX NAME)





REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2002 ACS

AB Soft capsules contain Et docosahexaenoate, Et eicosapentaenoate, other polyunsatd. fatty acid Et esters, soybean phospholipids, Oenothera odorata and ginkgetin at a ratio of (50:10:24:8:7:1)-(55:15:13:13:2:2) are useful as antithrombotic and antidementia agents for the treatment of e.g. **dementia** and myocardial infarction.

ACCESSION NUMBER: 1995:319841 CAPLUS
DOCUMENT NUMBER: 122:89398
TITLE: soft capsules containing ethyl docosahexaenoate and other ingredients for use as antithrombotic and antidementia agents
INVENTOR(S): Pan, Yuzhen; Liu, rongkui; Liu, Zhe
PATENT ASSIGNEE(S): Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 3 pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1082909	A	19940302	CN 1993-100040	19930103

AB . . . odorata and ginkgetin at a ratio of (50:10:24:8:7:1)-(55:15:13:13:2:2) are useful as antithrombotic and antidementia agents for the treatment of e.g. **dementia** and myocardial infarction.

IT Mental disorder
(**dementia**, soft capsules contg. Et docosahexaenoate and other ingredients for use as antithrombotic and antidementia agents)

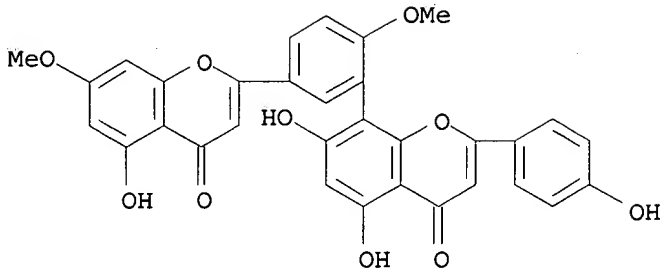
IT **481-46-9**, Ginkgetin 85354-43-4, Ethyl eicosapentaenoate 110508-33-3, Ethyl docosahexaenoate
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(soft capsules contg. Et docosahexaenoate and other ingredients for use as antithrombotic and antidementia agents)

IT **481-46-9**, Ginkgetin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(soft capsules contg. Et docosahexaenoate and other ingredients for use as antithrombotic and antidementia agents)

RN 481-46-9 CAPLUS

CN 4H-1-Benzopyran-4-one, 5,7-dihydroxy-8-[5-(5-hydroxy-7-methoxy-4-oxo-4H-1-benzopyran-2-yl)-2-methoxyphenyl]-2-(4-hydroxyphenyl)- (9CI) (CA INDEX NAME)

09/927,038



=>

```
=> s l6 and (neurit? or neurocyt?)
          1877 L6
         10047 NEURIT?
           319 NEUROCYT?
L8           1 L6 AND (NEURIT? OR NEUROCYT?)

=> d l8 abs ibib kwic hitstr 1
```

Structure + key terms

L8 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS

AB Polyalkoxyflavonoids, esp. nobiletin and tangeretin, in the Rutaceae ext. are useful for control and relief of neurodegenerative diseases such as cerebral ischemia. Dried peel of Citrus unshiu was extd. with ethanol and nobiletin and tangeretin identified in the ext. by known method. Biol. activity of the Citrus unshiu ext. on the PC12 cell was shown.

ACCESSION NUMBER: 2002:148735 CAPLUS
DOCUMENT NUMBER: 136:164277
TITLE: **Neurite** outgrowth factor in Rutaceae extract
INVENTOR(S): Ito, Hisatomi; Tamura, Shinya; Miyazaki, Toshiji
PATENT ASSIGNEE(S): Nagase and Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 9 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2002060340	A2	20020226	JP 2000-248021	20000817
US 2002040052	A1	20020404	US 2001-927038	20010809

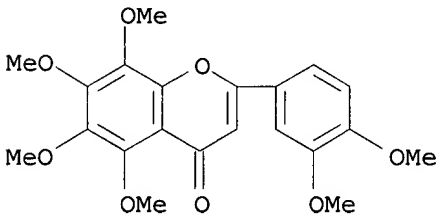
PRIORITY APPLN. INFO.: JP 2000-248021 A 20000817
OTHER SOURCE(S): MARPAT 136:164277

Appl.

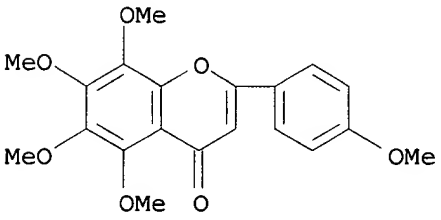
TI **Neurite** outgrowth factor in Rutaceae extract
ST Rutaceae ext **neurite** outgrowth factor neurodegenerative disease; polyalkoxyflavonoid neurodegenerative disease control Rutaceae ext
IT Nervous system
(degeneration; **neurite** outgrowth agent)
IT Brain, disease
(ischemia; **neurite** outgrowth agent)
IT Growth factors, animal
RL: PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**neurite** extension factors; **neurite** outgrowth agent)
IT Alzheimer's disease
Citrus depressa
Drugs
Health food
Rutaceae
Satsuma
(**neurite** outgrowth agent)
IT Flavonoids
RL: PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(polyalkoxyflavonoids; **neurite** outgrowth agent)
IT Orange
(sour; **neurite** outgrowth agent)

09/927,038

IT 64-17-5, Ethanol, uses
RL: NUU (Other use, unclassified); USES (Uses)
(**neurite** outgrowth agent)
IT **478-01-3P**, Nobiletin **481-53-8P**, Tangeretin
RL: PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**neurite** outgrowth agent)
IT **478-01-3P**, Nobiletin **481-53-8P**, Tangeretin
RL: PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**neurite** outgrowth agent)
RN 478-01-3 CAPLUS
CN 4H-1-Benzopyran-4-one, 2-(3,4-dimethoxyphenyl)-5,6,7,8-tetramethoxy- (9CI) (CA INDEX NAME)



RN 481-53-8 CAPLUS
CN 4H-1-Benzopyran-4-one, 5,6,7,8-tetramethoxy-2-(4-methoxyphenyl)- (9CI) (CA INDEX NAME)



=>

```
=> s (nobiletin? or tangeretin?)
           234 NOBILETIN?
           251 TANGERETIN?
L1         347 (NOBILETIN? OR TANGERETIN?)

=> s l1 and (neurit? or neurocyt?)
         10047 NEURIT?
           319 NEUROCYT?
L2           1 L1 AND (NEURIT? OR NEUROCYT?)

=> d l2 abs ibib kwic 1

L2   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2002 ACS
AB   Polyalkoxyflavonoids, esp. nobiletin and tangeretin,
     in the Rutaceae ext. are useful for control and relief of
     neurodegenerative diseases such as cerebral ischemia.  Dried peel of
     Citrus unshiu was extd. with ethanol and nobiletin and
     tangeretin identified in the ext. by known method.  Biol. activity
     of the Citrus unshiu ext. on the PC12 cell was shown.
ACCESSION NUMBER:         2002:148735  CAPLUS
DOCUMENT NUMBER:          136:164277
TITLE:                    Neurite outgrowth factor in Rutaceae extract
INVENTOR(S):              Ito, Hisatomi; Tamura, Shinya; Miyazaki, Toshiji
PATENT ASSIGNEE(S):       Nagase and Co., Ltd., Japan
SOURCE:                   Jpn. Kokai Tokkyo Koho, 9 pp.
                          CODEN: JKXXAF
DOCUMENT TYPE:            Patent
LANGUAGE:                 Japanese
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.   DATE
     ---------------   ----  --------       ---------------   --------
     JP 2002060340      A2   20020226       JP 2000-248021    20000817
     US 2002040052      A1   20020404       US 2001-927038    20010809
PRIORITY APPLN. INFO.:                  JP 2000-248021    A  20000817
OTHER SOURCE(S):          MARPAT 136:164277
TI   Neurite outgrowth factor in Rutaceae extract
AB   Polyalkoxyflavonoids, esp. nobiletin and tangeretin,
     in the Rutaceae ext. are useful for control and relief of
     neurodegenerative diseases such as cerebral ischemia.  Dried peel of
     Citrus unshiu was extd. with ethanol and nobiletin and
     tangeretin identified in the ext. by known method.  Biol. activity
     of the Citrus unshiu ext. on the PC12 cell was shown.
ST   Rutaceae ext neurite outgrowth factor neurodegenerative disease;
     polyalkoxyflavonoid neurodegenerative disease control Rutaceae ext
IT   Nervous system
        (degeneration; neurite outgrowth agent)
IT   Brain, disease
        (ischemia; neurite outgrowth agent)
IT   Growth factors, animal
     RL: PUR (Purification or recovery); THU (Therapeutic use); BIOL
     (Biological study); PREP (Preparation); USES (Uses)
        (neurite extension factors; neurite outgrowth
        agent)
IT   Alzheimer's disease
     Citrus depressa
```

Drugs
Health food
Rutaceae
Satsuma
(**neurite** outgrowth agent)

IT Flavonoids
RL: PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(polyalkoxyflavonoids; **neurite** outgrowth agent)

IT Orange
(sour; **neurite** outgrowth agent)

IT 64-17-5, Ethanol, uses
RL: NUU (Other use, unclassified); USES (Uses)
(**neurite** outgrowth agent)

IT 478-01-3P, **Nobiletin** 481-53-8P, **Tangeretin**
RL: PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**neurite** outgrowth agent)

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=> s l1 and (neurodegenerat? or alzheimer? or dementi? or ischem?)
         11330 NEURODEGENERAT?
         24330 ALZHEIMER?
          7530 DEMENTI?
         57712 ISCHEM?
L3            4 L1 AND (NEURODEGENERAT? OR ALZHEIMER? OR DEMENTI? OR ISCHEM?)

=> d l3 abs ibib kwic 1-4

L3   ANSWER 1 OF 4  CAPLUS  COPYRIGHT 2002 ACS
AB   Polyalkoxyflavonoids, esp. nobiletin and tangeretin,
     in the Rutaceae ext. are useful for control and relief of
     neurodegenerative diseases such as cerebral ischemia.
     Dried peel of Citrus unshiu was extd. with ethanol and nobiletin
     and tangeretin identified in the ext. by known method.  Biol.
     activity of the Citrus unshiu ext. on the PC12 cell was shown.
ACCESSION NUMBER:         2002:148735  CAPLUS
DOCUMENT NUMBER:          136:164277
TITLE:                    Neurite outgrowth factor in Rutaceae extract
INVENTOR(S):              Ito, Hisatomi; Tamura, Shinya; Miyazaki, Toshiji
PATENT ASSIGNEE(S):       Nagase and Co., Ltd., Japan
SOURCE:                   Jpn. Kokai Tokkyo Koho, 9 pp.
                          CODEN: JKXXAF
DOCUMENT TYPE:            Patent
LANGUAGE:                 Japanese
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE          APPLICATION NO.   DATE
     ---------------   ----  --------      ---------------   --------
     JP 2002060340      A2   20020226      JP 2000-248021    20000817
     US 2002040052      A1   20020404      US 2001-927038    20010809
PRIORITY APPLN. INFO.:                  JP 2000-248021    A 20000817
OTHER SOURCE(S):          MARPAT 136:164277
AB   Polyalkoxyflavonoids, esp. nobiletin and tangeretin,
     in the Rutaceae ext. are useful for control and relief of
     neurodegenerative diseases such as cerebral ischemia.
     Dried peel of Citrus unshiu was extd. with ethanol and nobiletin
```

and **tangeretin** identified in the ext. by known method. Biol. activity of the Citrus unshiu ext. on the PC12 cell was shown.

ST Rutaceae ext neurite outgrowth factor **neurodegenerative** disease; polyalkoxyflavonoid **neurodegenerative** disease control Rutaceae ext

IT Brain, disease
(**ischemia**; neurite outgrowth agent)

IT **Alzheimer**'s disease
Citrus depressa
Drugs
Health food
Rutaceae
Satsuma
(neurite outgrowth agent)

IT 478-01-3P, **Nobiletin** 481-53-8P, **Tangeretin**
RL: PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(neurite outgrowth agent)

L3 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2002 ACS

AB This invention relates to the use of flavone or derivs. thereof for the treatment of diseases mediated by cyclooxygenase-2 or NF.kappa.B. The flavones can be administered in oral dosage forms or foods.

ACCESSION NUMBER: 2001:626002 CAPLUS
DOCUMENT NUMBER: 135:185492
TITLE: Flavones for the treatment of COX-2 and/or NF.kappa.B-mediated diseases
INVENTOR(S): Wenzel, Uwe; Daniel, Hannelore
PATENT ASSIGNEE(S): Basf A. -G., Germany
SOURCE: Jpn. Kokai Tokkyo Koho, 13 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2001233768	A2	20010828	JP 2001-49370	20010223
EP 1127572	A2	20010829	EP 2001-103200	20010212
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 2001046963	A1	20011129	US 2001-782306	20010214
CN 1318371	A	20011024	CN 2001-116513	20010225

PRIORITY APPLN. INFO.: US 2000-185179P P 20000225
OTHER SOURCE(S): MARPAT 135:185492

IT Adhesion, biological
Analgesics
Anti-**Alzheimer**'s agents
Anti-inflammatory agents
Antiarthritics
Antidiabetic agents
Antipyretics
Antirheumatic agents
Beverages
Breakfast cereal
Milk preparations
Nutrients

(flavones for treatment of COX-2 and/or NF.kappa.B-mediated diseases)
IT 481-53-8, **Tangeretin** 486-66-8, Daidzein 487-26-3, Flavanone 491-54-3, Kaempferide 491-67-8, Baicalein 491-70-3, Luteolin 491-80-5, Biochanin 520-26-3, Hesperidin 520-27-4, Diosmin 520-33-2, Hesperetin 525-82-6, Flavone 528-48-3, Fisetin 529-44-2, Myricetin 529-59-9, Genistin 577-85-5, 3-Hydroxyflavone 14259-47-3, Didymin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); FFD (Food or feed use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(flavones for treatment of COX-2 and/or NF.kappa.B-mediated diseases)

L3 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2002 ACS
AB Beadlets comprising xanthophylls and carotenes and/or retinoids, dietary supplements comprising these beadlets and methods of use are disclosed.
ACCESSION NUMBER: 2001:208119 CAPLUS
DOCUMENT NUMBER: 134:236643
TITLE: Stable carotene-xanthophyll beadlet compositions and methods of use
INVENTOR(S): Lang, John C.
PATENT ASSIGNEE(S): Alcon Universal Ltd., Switz.
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001019383	A1	20010322	WO 2000-US24439	20000906
W: AU, BR, CA, JP, MX, TR, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1212071	A1	20020612	EP 2000-959942	20000906
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				

PRIORITY APPLN. INFO.: US 1999-397472 A 19990917
WO 2000-US24439 W 20000906
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
IT Eye, disease
(retina, **ischemia**; stable carotene-xanthophyll beadlet compns. and methods of use)
IT 57-50-1, Sucrose, biological studies 59-30-3, Folic acid, biological studies 59-67-6, Niacin, biological studies 65-23-6, Pyridoxine 68-19-9, Cyanocobalamin 79-83-4, Pantothenic acid 83-88-5, Vitamin B2, biological studies 110-44-1, Sorbic acid 117-39-5, Quercetin 127-40-2, Lutein 137-66-6, Ascorbyl palmitate 144-68-3, Zeaxanthin 153-18-4, Rutin 472-61-7, Astaxanthin 472-70-8, Cryptoxanthin 472-89-9, .epsilon.-Carotene 472-92-4, .delta.-Carotene 472-93-5, .gamma.-Carotene 478-01-3, **Nobiletin** 480-18-2 480-40-0, Chrysin 480-44-4, Acacetin 481-53-8, **Tangeretin** 502-65-8, .psi.,.psi.-Carotene 514-78-3, Canthaxanthin 520-18-3, Kaempferol 520-36-5, Apigenin 532-32-1, Sodium benzoate 551-15-5, Liquiritin 557-04-0, Magnesium stearate 557-34-6, Zinc acetate 1406-18-4, Vitamin E 3211-76-5, L-Selenomethionine 4345-03-3, .alpha.-Tocopherol succinate 7235-40-7, .beta.-Carotene 7439-96-5, Manganese, biological studies 7440-47-3, Chromium, biological studies 7440-50-8, Copper,

biological studies 7440-50-8D, Copper, amino acid chelates, biological studies 7488-99-5, .alpha.-Carotene 7631-86-9, Silica, biological studies 7757-93-9, Dicalcium phosphate 7782-49-2, Selenium, biological studies 9004-65-3, Hydroxypropylmethylcellulose 9005-25-8, Starch, biological studies 9005-65-6, Polysorbate 80 13463-67-7, Titanium dioxide, biological studies 25322-68-3, Polyethylene glycol 74811-65-7, Croscarmellose sodium
RL: FFD (Food or feed use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stable carotene-xanthophyll beadlet compns. and methods of use)

L3 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2002 ACS

AB Various dietary flavonoids were evaluated in vitro for their inhibitory effect on xanthine oxidase, which has been implicated in oxidative injury to tissue by **ischemia**-reperfusion. Xanthine oxidase activity was detd. by directly measuring uric acid formation by HPLC. The structure-activity relationship revealed that the planar flavones and flavonols with a 7-hydroxyl group such as chrysin, luteolin, kaempferol, quercetin, myricetin, and isorhamnetin inhibited xanthine oxidase activity at low concns. (IC50 values from 0.40 to 5.02 .mu.M) in a mixed-type mode, while the nonplanar flavonoids, isoflavones and anthocyanidins were less inhibitory. These results suggest that certain flavonoids might suppress in vivo the formation of active oxygen species and urate by xanthine oxidase.

ACCESSION NUMBER: 1999:725048 CAPLUS
DOCUMENT NUMBER: 132:44494
TITLE: Inhibition of xanthine oxidase by flavonoids
AUTHOR(S): Nagao, Akihiko; Seki, Michiko; Kobayashi, Hidetaka
CORPORATE SOURCE: National Food Research Institute, Ministry of Agriculture, Forestry and Fisheries, Tsukuba, 305-8642, Japan
SOURCE: Bioscience, Biotechnology, and Biochemistry (1999), 63(10), 1787-1790
CODEN: BBBIEJ; ISSN: 0916-8451
PUBLISHER: Japan Society for Bioscience, Biotechnology, and Agrochemistry
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Various dietary flavonoids were evaluated in vitro for their inhibitory effect on xanthine oxidase, which has been implicated in oxidative injury to tissue by **ischemia**-reperfusion. Xanthine oxidase activity was detd. by directly measuring uric acid formation by HPLC. The structure-activity relationship revealed that the planar flavones and flavonols with a 7-hydroxyl group such as chrysin, luteolin, kaempferol, quercetin, myricetin, and isorhamnetin inhibited xanthine oxidase activity at low concns. (IC50 values from 0.40 to 5.02 .mu.M) in a mixed-type mode, while the nonplanar flavonoids, isoflavones and anthocyanidins were less inhibitory. These results suggest that certain flavonoids might suppress in vivo the formation of active oxygen species and urate by xanthine oxidase.

IT Antioxidants
Ischemia
Structure-activity relationship
(structure-related inhibition of xanthine oxidase by flavonoids)

IT 60-82-2, Phloretin 90-19-7, Rhamnetin 117-39-5, Quercetin 134-01-0, Peonidin 134-04-3, Pelargonidin 153-18-4, Rutin 154-23-4, + Catechin

446-72-0, Genistein 480-18-2, Taxifolin 480-19-3, Isorhamnetin
480-40-0, Chrysin 481-53-8, **Tangeretin** 486-66-8, Daidzein
487-26-3, Flavanone 490-46-0, -Epicatechin 491-70-3, Luteolin
520-18-3, KAempferol 520-33-2, Hesperitin 525-82-6, Flavone
528-53-0, Delphinidin 528-58-5, Cyanidin 529-44-2, Myricetin
574-12-9, Isoflavone 577-85-5, Flavonol 863-03-6, -Epicatechin gallate
970-74-1, -Epigallocatechin 989-51-5, (-)-Epigallocatechin gallate
1151-98-0, Apigenidin 1481-83-0, 3-Flavanol 1621-55-2 14051-53-7
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(structure-related inhibition of xanthine oxidase by flavonoids)

=>

FILE 'CAPLUS' ENTERED AT 18:38:00 ON 13 DEC 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE 'USPATFULL' ENTERED AT 18:38:00 ON 13 DEC 2002

=> d his

(FILE 'HOME' ENTERED AT 18:36:52 ON 13 DEC 2002)

FILE 'REGISTRY' ENTERED AT 18:37:11 ON 13 DEC 2002
L1 STRUCTURE UPLOADED
L2 50 S L1 SSS SAM
L3 3313 S L1 SSS FULL

FILE 'CAPLUS, USPATFULL' ENTERED AT 18:38:00 ON 13 DEC 2002

=> s l3 and (neurit? or neurocyt?) and (neurodegenerat? or alzheimer? or dementia? or ischem?)
L4 4 L3 AND (NEURIT? OR NEUROCYT?) AND (NEURODEGENERAT? OR ALZHEIMER? OR DEMENTIA? OR ISCHEM?)

=> dup rem l4
PROCESSING COMPLETED FOR L4
L5 4 DUP REM L4 (0 DUPLICATES REMOVED)

=> d l5 abs ibib kwic hitstr 1-4

L5 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2002 ACS
AB Polyalkoxyflavonoids, esp. nobiletin and tangeretin, in the Rutaceae ext. are useful for control and relief of **neurodegenerative** diseases such as cerebral **ischemia**. Dried peel of Citrus unshiu was extd. with ethanol and nobiletin and tangeretin identified in the ext. by known method. Biol. activity of the Citrus unshiu ext. on the PC12 cell was shown.
ACCESSION NUMBER: 2002:148735 CAPLUS
DOCUMENT NUMBER: 136:164277
TITLE: **Neurite** outgrowth factor in Rutaceae extract
INVENTOR(S): Ito, Hisatomi; Tamura, Shinya; Miyazaki, Toshiji
PATENT ASSIGNEE(S): Nagase and Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 9 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2002060340	A2	20020226	JP 2000-248021	20000817
US 2002040052	A1	20020404	US 2001-927038	20010809

PRIORITY APPLN. INFO.: JP 2000-248021 A 20000817
OTHER SOURCE(S): MARPAT 136:164277
TI **Neurite** outgrowth factor in Rutaceae extract
AB Polyalkoxyflavonoids, esp. nobiletin and tangeretin, in the Rutaceae ext.

are useful for control and relief of **neurodegenerative** diseases such as cerebral **ischemia**. Dried peel of Citrus unshiu was extd. with ethanol and nobiletin and tangeretin identified in the ext. by known method.. . .

ST Rutaceae ext **neurite** outgrowth factor **neurodegenerative** disease; polyalkoxyflavonoid **neurodegenerative** disease control Rutaceae ext

IT Nervous system
(degeneration; **neurite** outgrowth agent)

IT Brain, disease
(**ischemia**; **neurite** outgrowth agent)

IT Growth factors, animal
RL: PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**neurite** extension factors; **neurite** outgrowth agent)

IT **Alzheimer**'s disease
Citrus depressa
Drugs
Health food
Rutaceae
Satsuma
(**neurite** outgrowth agent)

IT Flavonoids
RL: PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(polyalkoxyflavonoids; **neurite** outgrowth agent)

IT Orange
(sour; **neurite** outgrowth agent)

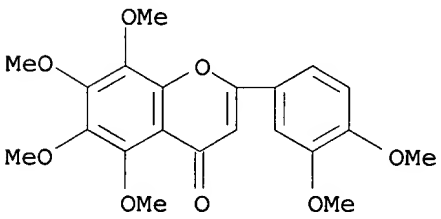
IT 64-17-5, Ethanol, uses
RL: NUU (Other use, unclassified); USES (Uses)
(**neurite** outgrowth agent)

IT **478-01-3P**, Nobiletin **481-53-8P**, Tangeretin
RL: PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**neurite** outgrowth agent)

IT **478-01-3P**, Nobiletin **481-53-8P**, Tangeretin
RL: PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**neurite** outgrowth agent)

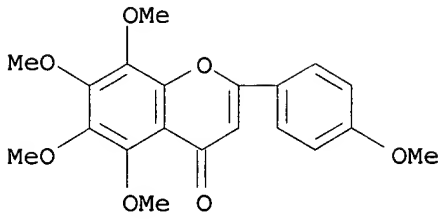
RN 478-01-3 CAPLUS

CN 4H-1-Benzopyran-4-one, 2-(3,4-dimethoxyphenyl)-5,6,7,8-tetramethoxy- (9CI) (CA INDEX NAME)



RN 481-53-8 CAPLUS

CN 4H-1-Benzopyran-4-one, 5,6,7,8-tetramethoxy-2-(4-methoxyphenyl)- (9CI) (CA INDEX NAME)



L5 ANSWER 2 OF 4 USPATFULL

AB The present invention relates to methods for extending **neurites**, using a composition containing a polyalkoxyflavonoid having a specific structure, especially nobiletin or tangeretin. It is found that also a composition containing an extract from a plant belonging to the citrus family has an activity to extend **neurites**. These compositions are useful to prevent and/or improve or treat **neurodegeneration** diseases such as **Alzheimer**'s **dementia** and encephalic **ischemia** by accelerating extension of **neurites**.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2002:72912 USPATFULL
TITLE: Method for **neurite** outgrowth
INVENTOR(S): Ito, Hisatomi, Kobe, JAPAN
Tamura, Shinya, Kobe, JAPAN
Miyazaki, Toshitsugu, Kobe, JAPAN

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002040052	A1	20020404	
APPLICATION INFO.:	US 2001-927038	A1	20010809	(9)

	NUMBER	DATE
PRIORITY INFORMATION:	JP 2000-248021	20000817

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: AMIN & TUROCY, LLP, 1900 EAST 9TH STREET, NATIONAL CITY CENTER, 24TH FLOOR,, CLEVELAND, OH, 44114
NUMBER OF CLAIMS: 15
EXEMPLARY CLAIM: 1
LINE COUNT: 701

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Method for **neurite** outgrowth

AB The present invention relates to methods for extending **neurites**, using a composition containing a polyalkoxyflavonoid having a specific structure, especially nobiletin or tangeretin. It is found that also a composition containing an extract from a plant belonging to the citrus family has an activity to extend **neurites**. These compositions are useful to prevent and/or improve or treat **neurodegeneration** diseases such as **Alzheimer**'s **dementia** and encephalic **ischemia** by accelerating extension of **neurites**.

SUMM [0002] The present invention relates to methods for extending **neurites** of **neurocytes** and compositions having **neurite** extending effect. More specifically, the present

invention relates to methods for preventing and/or improving or treating **neurodegeneration** diseases such as **Alzheimer**'s **dementia** and cerebral **ischemia** by accelerating **neurite** extension, and compositions for extending **neurites** that are useful for these methods.

SUMM [0004] With the shift to the aging society, the incidence of senile **dementia** has been increasing and this has become a serious social problem. Many diseases are known to cause senile **dementia** . Senile **dementia** is roughly classified into three types: **dementia** due to organic disorders of the brain; **dementia** associated with diseases of organs other than brain; and **dementia** due to physical diseases caused by stress. In particular, senile **dementia** is caused mostly by organic disorders of the brain, and the **dementia** of this type is further classified into two types, cerebrovascular **dementia** and **Alzheimer**'s **dementia**, depending on its cause.

SUMM [0005] It is known today that cerebral vasodilators have some effect on cerebrovascular **dementia**. However, concerning **Alzheimer**'s **dementia**, the cause of this disease is still unknown and there is no report on treatment methods or pharmacotherapy suitable to. . . as well as its advance. Therefore, there is a need to develop medicines that are effective with respect to the **dementia** caused by organic disorders of the brain, especially **Alzheimer**'s **dementia**.

SUMM [0006] In recent years, neurotrophical factors secreted from **neurocytes** such as nerve growth factors (NGF) have been found to exhibit excellent effects on **neurodegeneration** diseases and have attracted public attention. An NGF is a factor that is important and necessary for nervous tissue to. . . the peripheral nerves, and of magnocellular cholinergic neuron in the central nerves. An NGF also acts to prevent degeneration of **neurocytes** when the brain is damaged. In this regard, raising the NGF level in a living body seems to be effective as a treatment method for disorders of central function, such as **Alzheimer**'s **dementia** and cerebrovascular **dementia**, spinal cord injuries, peripheral nerve injuries, diabetic neuropathy and disorder of peripheral function such as amyotrophic lateral sclerosis.

SUMM [0010] Therefore, in order to prevent and/or improve or treat senile **dementia**, low molecular weight substances that exhibit NGF-like activity appear to be effective.

SUMM . . . inhibitory effect. Japanese Laid-Open Patent Publication (Tokkai) No.6-31627 has reported that alcoholic extracts of ginseng have an activating effect on **neurocytes**, but the substance that has the activating effect has not been specified.

SUMM . . . Therefore, with the foregoing in mind, it is an object of the present invention to provide a method for extending **neurites** of **neurocytes** without any side effects, and a method for preventing and/or treating **neurodegeneration** diseases using novel compositions having **neurite** extending effect.

SUMM [0013] The present invention provides a method for extending **neurites** including administering a composition to a subject, the composition including a polyalkoxyflavonoid represented by Formula 1, and a pharmaceutically acceptable. . .

SUMM [0015] The present invention also provides a method for extending **neurites** including administering a composition to a subject, the composition including an extract of a plant belonging to the citrus family,. . .

SUMM [0016] The present invention also provides a method for preventing

and/or treating **neurodegeneration** diseases including administering a composition to a subject, the composition including a polyalkoxyflavonoid represented by Formula 1, and a pharmaceutically. . .

SUMM [0018] The present invention also provides a method for preventing and/or treating **neurodegeneration** diseases including administering a composition to a subject, the composition including an extract of a plant belonging to the citrus. . .

SUMM [0019] The present invention further provides a method for extending **neurites** including bringing a composition in contact with **neurocytes**, the composition including a polyalkoxyflavonoid represented by Formula 1 and a physiologically acceptable carrier: ##STR3##

SUMM [0021] The present invention further provides a method for extending **neurites** including bringing a composition in contact with **neurocytes**, the composition including an extract of a plant belonging to the citrus family and a physiologically acceptable carrier.

SUMM . . . the present invention, the present invention provides a composition that is a pharmaceutical composition or a quasi-drug composition for extending **neurites** or for preventing and/or treating **neurodegeneration** diseases and contains a polyalkoxyflavonoid represented by Formula 1 or an extract from a plant belonging to the citrus family. . .

SUMM [0026] The present invention also provides a composition that is a food composition for extending **neurites** or preventing and/or treating **neurodegeneration** diseases and contains a polyalkoxyflavonoid represented by Formula 1 or an extract from a plant belonging to the citrus family. . .

SUMM [0028] The present invention further provides a composition that is a composition for cell treatment to extend **neurites** of **neurocytes** and contains a polyalkoxyflavonoid represented by Formula 1 or an extract from a plant belonging to the citrus family, and. . .

SUMM [0032] According to the present invention, a composition that is highly safe and has excellent **neurite** extending effect on cells can be provided, and therefore, a method for extending **neurites** and a method for preventing and/or treating **neurodegeneration** diseases are provided. In particular, it is effective to use a composition containing nobiletin or tangeretin that is a polyalkoxyflavonoid as an active ingredient. The composition for extending **neurites** of the present invention can be used as a pharmaceutical, a quasi-drug or a food, and are effective to extend **neurites** and to prevent and/or treat **neurodegeneration** diseases such as **Alzheimer**'s **dementia** and encephalic **ischemia**.

SUMM [0034] It is known that PC12 cells derived from adrenal medulla pheochromocytoma of rats extend **neurites** in response to NGFs. The inventors of the present invention examined various substances having NGF-like activities, using an evaluation system. . . a result, the inventors of the present invention discovered that a polyalkoxyflavonoid having a specific chemical structure exhibits an excellent **neurite** extending effect.

SUMM [0035] In the present invention, "a composition for extending **neurites**" refers to a composition containing extracts of plants belonging to the citrus family or a composition containing a polyalkoxyflavonoid as. . .

SUMM . . . less, more preferably about 30% by weight or less. If the polyalkoxyflavonoid content is less than 0.00001% by weight, the

neurite extending effect may not reach the desired level. On the other hand, if the content exceeds 50% by weight, better. . .

SUMM [0056] By using the compositions of the present invention obtained in the above-described manner, it is possible to extend **neurites** or prevent and/or treat **neurodegeneration** diseases.

SUMM . . . for example in vitro, by culturing cells in a medium containing the composition for cell treatment of the present invention, **neurite** extension of the cells can be observed. In vivo, by orally administrating the pharmaceutical composition of the present invention, **neurite** extension is accelerated, and furthermore, the prevention and/or treatment of **neurodegeneration** diseases such as **Alzheimer**'s **dementia** and encephalic **ischemia** can be expected. The dose of the composition of the present invention, both in vitro and in vivo, can be. . .

DETD . . . the above substances nobiletin and tangeretin was used without any further treatment as a test material A (composition for extending **neurites**).

DETD . . . microscopic observation was conducted with respect to the cells at 200 times magnification. The percentage of the cells with extended **neurites** (cells that have **neurites** longer than their diameter) to the total of more than 200 cells was calculated. The results are shown in Table. . .

DETD [0070] The percentage of the cells with extended **neurites** was calculated in the same manner as in Example 1 except that PC12 cells were transferred to the DEMEM-TIP medium. . .

DETD [0073] The percentage of the cells with extended **neurites** was calculated in the same manner as in Example 1 except that the extract from Citrus depressa was used without. . .

DETD [0074] The percentage of the cells with extended **neurites** was calculated in the same manner as in Example 3 except that PC12 cells were transferred to the DEMEM-TIP medium. . .

DETD [0077] The percentage of the cells with extended **neurites** was calculated in the same manner as in Example 1 except that the extract from Citrus aurantium was used without. . .

DETD [0078] The percentage of the cells with extended **neurites** was calculated in the same manner as in Example 5 except that PC12 cells were transferred to the DEMEM-TIP medium. . .

DETD [0079] The percentage of the cells with extended **neurites** was calculated in the same manner as in Example 1 except that nobiletin obtained in Example 1 was used without. . .

DETD [0080] The percentage of the cells with extended **neurites** was calculated in the same manner as in Example 1 except for using nobiletin obtained in Example 1 was used. . .

DETD [0081] The percentage of the cells with extended **neurites** was calculated in the same manner as in Example 1 except that nobiletin obtained in Example 1 was used without. . .

DETD [0082] The percentage of the cells with extended **neurites** was calculated in the same manner as in Example 1 except that tangeretin obtained in Example 1 was used without. . .

DETD [0083] The percentage of the cells with extended **neurites** was calculated in the same manner as in Example 1 except tangeretin obtained in Example 1 was used without any. . .

DETD [0084] The percentage of the cells with extended **neurites** was calculated in the same as in Example 1 except that PC12 cells were transferred to the DEMEM-TIP medium that. . .

DETD [0085] The percentage of the cells with extended **neurites** was calculated in the same manner as in Example 1 except that dibutyl cyclic (manufactured by Sigma Inc.) that has been reported to have

neurite extending effect (Neurochem. Int. 33, 503, (1999)) was used without any further treatment as a test material F instead of. . .

DETD [0086] The percentage of the cells with extended **neurites** was calculated in the same manner as in Example 1 except that isobutylmethylxanthine (manufactured by Sigma Inc.) that has been reported to have **neurite** extending effect (J. Neurobiol. 19 (8), 681, (1988)) was used without any further treatment as a test material G instead. . . Ratio of a composition for extending **neurites** of the present invention

	Active ingredient in the test material	in the medium	of the cells with extended **neurites** to the cells with extended **neurites** (%)	ratio of the cells with extended **neurites** to control (Com. Ex. 1).sup.1)
Ex. 1	extract of immature peel of Citrus. . .	10 .mu.g/ml	10.2	2.9
Ex. 3	xanthine	100 .mu.M	11.8	3.4

.sup.1) Relative value is the value obtained by dividing "the percentage of the cells with extended **neurites**" by the control value (Comparative Example 1).

DETD . . . of Comparative Example 1, all of the test materials A to E used in Examples 1 to 11 have excellent **neurite** extending effect to cells. According to the results of Examples 1 to 11, the higher concentration the test materials that are added to the cells have, the greater the **neurite** extending effect is. These values are equivalent or more than the results of test materials F and G known to have **neurite** extending activity in Comparative Examples 2 and 3. From this regard, it is evident that all of the test materials A to E used in Examples 1 to 11 are useful as compositions for extending **neurites**.

CLM What is claimed is:

1. A method for extending **neurites** comprising administering a composition to a subject, the composition comprising a polyalkoxyflavonoid represented by Formula 1, and a pharmaceutically acceptable. . .

3. A method for extending **neurites** comprising administering a composition to a subject, the composition comprising an extract from a plant belonging to the citrus family,. . .

6. A method for preventing and/or treating **neurodegeneration** diseases comprising administering a composition to a subject, the composition comprising a polyalkoxyflavonoid represented by Formula 1, and a pharmaceutically. . .

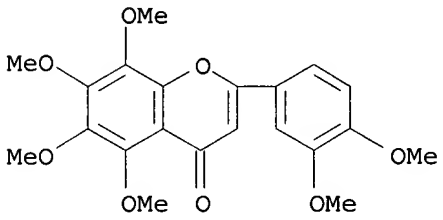
8. A method for preventing and/or treating **neurodegeneration** diseases comprising administering a composition to a subject, the composition comprising an extract from a plant belonging to the citrus. . .

11. A method for extending **neurites** comprising bringing a composition in contact with **neurocytes**, the composition comprising a polyalkoxyflavonoid represented by Formula 1, and a physiologically acceptable carrier: ##STR13## wherein R.sub.1 is H or. . .

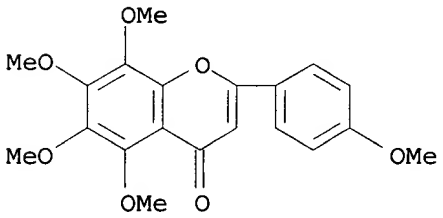
13. A method for extending **neurites** comprising bringing a composition in contact with **neurocytes**, the composition

comprising an extract from a plant belonging to the citrus family, and a physiologically acceptable carrier.

IT **478-01-3P**, Nobiletin **481-53-8P**, Tangeretin
(neurite outgrowth agent)
IT **478-01-3P**, Nobiletin **481-53-8P**, Tangeretin
(neurite outgrowth agent)
RN 478-01-3 USPATFULL
CN 4H-1-Benzopyran-4-one, 2-(3,4-dimethoxyphenyl)-5,6,7,8-tetramethoxy- (9CI) (CA INDEX NAME)



RN 481-53-8 USPATFULL
CN 4H-1-Benzopyran-4-one, 5,6,7,8-tetramethoxy-2-(4-methoxyphenyl)- (9CI) (CA INDEX NAME)



L5 ANSWER 3 OF 4 USPATFULL
AB A method is provided for therapeutic use of a class of compounds that are effective in protecting nerve cells from deterioration and cell death arising from degenerative disease, trauma or aging and may be used to achieve a similar effect in male and female subjects with minimal adverse side effects. The method comprises administering a therapeutically effective dose of a natural or synthetic bioflavonoid that acts as an MAPK cascade antagonist. Examples of bioflavonoids that may be used in the present method are apigenin and 2-(2'-amino-3' methoxyphenyl)-oxanaphthalen-4-one (PD098059).

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2002:239045 USPATFULL
TITLE:	Neuroprotective effects of mitogen-activated protein kinase (MAPK) cascade inhibitors
INVENTOR(S):	Baskys, Andrius, 10 Cool Brook, Irvine, CA, United States 92612

NUMBER	KIND	DATE

09/927,038

PATENT INFORMATION:	US 6451837	B1	20020917
APPLICATION INFO.:	US 2000-653065		20000901 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-151955P	19990901 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Gitomer, Ralph
ASSISTANT EXAMINER: Khare, Devesh
LEGAL REPRESENTATIVE: Cummings & Lockwood LLC
NUMBER OF CLAIMS: 11
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 6 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT: 797
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . achieve neuroprotection of cells in the central nervous system from death and for stimulating nerve cell survival in subjects with **neurodegenerative** disorders.

SUMM . . . ongoing death of nerve cells in the central nervous system are prevalent in today's society and include acute or chronic **neurodegenerative** disorders. An example of a chronic **neurodegenerative** disorder is **Alzheimer**'s disease. Other examples of **neurodegenerative** disorders include Parkinson's disease; Huntington's disease; AIDS **Dementia**; Wernicke-Korsakoff's related **dementia** (alcohol induced **dementia**); age related **dementia**; age associated memory impairment; brain cell loss due to head trauma, stroke, hypoglycemia, **ischemia**, anoxia, hypoxia, cerebral edema, arteriosclerosis, hematoma or epilepsy; spinal cord cell loss due to any of the conditions listed under brain cell loss; and peripheral neuropathy. Chronic and acute **neurodegenerative** diseases and acute nerve cell injury, as well as associated mortality and morbidity, have been largely untreatable with previous methods.. . . Accordingly, effective therapeutic approaches directed to the prevention or reduction of nerve cell death or nerve cell damage associated with **neurodegenerative** diseases and acute nerve cell injury are needed. Specifically, an efficacious method for treating conditions in the brain resulting from. . .

SUMM . . . caused by such overstimulation is referred to as "excitotoxicity." Excitotoxicity is thought to be important in the pathogenesis of several **neurodegenerative** disorders, including stroke and **ischemic** injury. Excitotoxicity has been studied in vivo and in vitro, including in organotypic hippocampal explant preparations. Excitotoxicity is caused by. . . kinase C ("PKC"). It has been shown that inhibition or reduction of PKC formation protects against nerve cell death following **ischemia**.

SUMM . . . multitude of mechanisms including cell differentiation and response to injury. PKC is abundant in neurons. It has been established that **ischemia** affects PKC activity and distribution. **Ischemic** nerve cell death has been associated with induction of PKC-delta isozyme. This effect can be blocked by NMDA inhibitors. Increased PKC-gamma immunoreactivity following incomplete **ischemia** has been found in the hippocampus. It has been shown that NMDA receptor stimulation can trigger PKC-gamma and beta isozyme. . .

SUMM Exposure of cells to stress activates protein kinases by a variety of mechanisms. For example, **ischemia**, NMDA and amyloid peptides

activate MAPK. Studies of functional roles of MAPKs in nerve tissue suggest that MAPK could be. . .

SUMM **Alzheimer**'s Disease (AD) is a progressive **neurodegenerative** disease which is histologically characterized by an accumulation of **neuritic** plaques and neurofibrillary tangles and by neuron death. A major component of these **neuritic** plaques is the .beta.-protein, which is derived from a precursor protein called the .beta.-amyloid precursor protein (APP). The .beta.-amyloid protein. . .

SUMM . . . where such compounds could be used in the treatment of the chronic as well as the acute conditions caused by **neurodegenerative** diseases, trauma, and aging at non-toxic dosages.

DETD "**Neurodegenerative** disorder" is defined here and in the claims as a disorder in which progressive loss of neurons occurs either in the peripheral nervous system or in the central nervous system. Examples of **neurodegenerative** disorders include: chronic **neurodegenerative** diseases such as **Alzheimer**'s disease, Parkinson's disease, Huntington's chorea, diabetic peripheral neuropathy, multiple sclerosis, amyotrophic lateral sclerosis; aging; and acute **neurodegenerative** disorders including: stroke, traumatic brain injury, schizophrenia, peripheral nerve damage, hypoglycemia, spinal cord injury, epilepsy, and anoxia and hypoxia. These. . . are not meant to be comprehensive or limiting in any way but serve merely as an illustration of the term " **neurodegenerative** disorder."

DETD . . . as the MAPK cascade. The method is used for treating and preventing nerve cell death caused by acute or chronic **neurodegenerative** disorders. The method comprises supplying at least one bioflavonoid that acts as an inhibitor of intracellular enzymes, such as MAPK,. . .

DETD . . . dose" means a dose of a MAPK cascade inhibitor which will treat or protect a subject from acute or chronic **neurodegenerative** disorders such as for example **Alzheimer**'s disease. Therapeutically effective doses of the MAPK cascade inhibitor can be determined according to standard medical principles under the direction. . .

DETD Cardell M. and Wieloch T. Time course of the translocation and inhibition of protein kinase C during complete cerebral **ischemia** in the rat. J. Neurochem., 61,1308, 1993.

DETD Choi, D. W. and Rothman, S. M., The role of glutamate neurotoxicity in hypoxiic **ischemic** neuronal death, Annu. Rev. Neurosci., 13, 171, 1990.

DETD Coyle J. T and Puttfarken P. Oxidative stress, glutamate, and **neurodegenerative** disorders. Science, 262, 689, 1993.

DETD . . . N, Aftabuddin M., Moriwaki A and Hori Y. Immunocytochemical distribution of gamma isoform of protein kinase C (PKC-gamma) following incomplete **ischemia**. Indian J. Physiol. Pharmacol., 39, 37, 1995.

DETD Mattson M. P. Evidence for the involvement of protein kinase C in **neurodegenerative** changes in cultured human cortical neurons. Exp. Neurol., 112, 95, 1991.

DETD . . . J., Kang Y., Xu E. and Schleien C. L. Mitogen-activated protein (MAP) kinase activity during and after transient focal cerebral **ischemia** in rats. Soc. Neurosci. Abs., 24 Pt. 1),223, 1998.

DETD . . . R. C. and Coyle T. J. Delayed protection by MK-801 and tetrodotoxin in a rat organotypic hippocampal culture model of **ischemia**. Stroke, 25, 457, 1994.

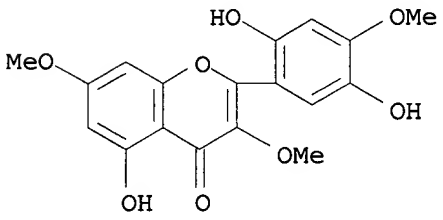
DETD Zablocka B and Domanska-Janik K. Involvement of protein kinase C in various cellular systems transducting **ischemia** evoked signal. Acta Neurobiol. Exp., 53, 25, 1993.

IT 90-19-7, Rhamnetin 117-39-5, Quercetin 153-18-4, Rutin 480-19-3, Isorhamnetin 482-36-0, Hyperin 482-38-2, Kaempferitrin 491-70-3, Luteolin 520-18-3, Pelargidenon 522-12-3, Quercitrin **549-17-7**, Oxyayanin-A 578-74-5, Cosmosiine 6601-62-3, Cirsimaritin 16290-07-6, Kaempferol-7-glucoside 17306-46-6, Rhoifolin 18003-33-3, 6-Hydroxyluteolin 21637-25-2, Isoquercitrin 21967-41-9, Baicalin 26046-94-6, Plantaginin 26544-34-3, Apiin 167869-21-8, PD098059 461015-54-3, Versulin 461015-55-4, Cossmetiin 461015-56-5, Sorbavin 461015-71-4, Afrelin
(neuroprotective effects of mitogen-activated protein kinase (MAPK) cascade inhibitors)

IT **549-17-7**, Oxyayanin-A
(neuroprotective effects of mitogen-activated protein kinase (MAPK) cascade inhibitors)

RN 549-17-7 USPATFULL

CN 4H-1-Benzopyran-4-one, 2-(2,5-dihydroxy-4-methoxyphenyl)-5-hydroxy-3,7-dimethoxy- (9CI) (CA INDEX NAME)



L5 ANSWER 4 OF 4 USPATFULL

AB Polyhydroxylated aromatic compounds, and compositions containing them, are useful for the treatment of amyloidosis, especially **Alzheimer**'s disease, and for the treatment of diseases characterized by .alpha.-synuclein fibril formation, especially Lewy body disease and Parkinson's disease.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2001:218540 USPATFULL

TITLE: Polyhydroxylated aromatic compounds for the treatment of amyloidosis and alpha-synuclein fibril diseases

INVENTOR(S): Castillo, Gerardo M., Seattle, WA, United States
Choi, Paula Y., Bothell, WA, United States
Snow, Alan D., Lynnwood, WA, United States

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2001047032	A1	20011129	
APPLICATION INFO.:	US 2000-748748	A1	20001226	(9)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 1999-173958P	19991230	(60)

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: HELLER EHRMAN WHITE & MCAULIFFE LLP, 275 MIDDLEFIELD

ROAD, MENLO PARK, CA, 94025-3506
NUMBER OF CLAIMS: 30
EXEMPLARY CLAIM: 1
LINE COUNT: 1536
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Polyhydroxylated aromatic compounds, and compositions containing them, are useful for the treatment of amyloidosis, especially **Alzheimer**'s disease, and for the treatment of diseases characterized by .alpha.-synuclein fibril formation, especially Lewy body disease and Parkinson's disease.

SUMM . . . invention relates to the use of certain polyhydroxylated aromatic compounds, and compositions containing them, for the treatment of amyloidosis, especially **Alzheimer**'s disease, and the treatment of diseases characterized by .alpha.-synuclein fibril formation, especially Lewy body disease and Parkinson's disease.

SUMM . . . classified according to the specific amyloid protein deposited. The amyloids include, but are not limited to, the amyloid associated with **Alzheimer**'s disease, Down's syndrome and hereditary cerebral hemorrhage with amyloidosis of the Dutch type (where the specific amyloid is referred to. . .

SUMM . . . a single organ or tissue such as observed with the AP amyloid deposits found in the brains of patients with **Alzheimer**'s disease and Down's syndrome: the PrP amyloid deposits found in the brains of patients with Creutzfeldt-Jakob disease, Gerstmann-Straussler syndrome, and. . .

SUMM [0009] **Alzheimer**'s Disease and the Aging Population

SUMM [0010] **Alzheimer**'s disease is a leading cause of **dementia** in the elderly, affecting 5-10% of the population over the age of 65 years (A Guide to Understanding **Alzheimer** 's Disease and Related Disorders, Jorm, ed., New York University Press, New York, 1987). In **Alzheimer**'s disease, the parts of the brain essential for cognitive processes such as memory, attention, language, and reasoning degenerate, robbing victims of much that makes us human, including independence. In some inherited forms of **Alzheimer**'s disease, onset is in middle age, but more commonly, symptoms appear from the mid-60's onward. **Alzheimer**'s disease today affects 4-5 million Americans, with slightly more than half of these people receiving care at home, while the others are in many different health care institutions. The prevalence of Aizheimer's disease and other **dementias** doubles every 5 years beyond the age of 65, and recent studies indicate that nearly 50% of all people age 85 and older have symptoms of **Alzheimer**'s disease (1999 Progress Report on **Alzheimer** 's Disease, National Institute on Aging/National Institute of Health). 13% (33 million people) of the total population of the United. . . are age 65 and older, and this percentage will climb to 20% by the year 2025 (1999 Progress Report on **Alzheimer**'s Disease).

SUMM [0011] **Alzheimer**'s disease also puts a heavy economic burden on society. A recent study estimated that the cost of caring for one **Alzheimer**'s disease patient with severe cognitive impairments at home or in a nursing home, is more than $47,000 per year (A Guide to Understanding **Alzheimer**'s Disease and Related Disorders). For a disease that can span from 2 to 20 years, the overall cost of **Alzheimer**'s disease to families and to society is staggering. The annual economic toll of **Alzheimer**'s disease in the United States in terms of health care expenses and lost wages of both patients and their caregivers is estimated at $80 to $100 billion (1999 Progress Report on **Alzheimer**'s Disease).

SUMM [0012] Tacrine hydrochloride ("Cognex"), the first FDA approved drug for **Alzheimer**'s disease, is a acetylcholinesterase inhibitor (Cutler and Sramek, N. Engl. J Med. 328:808 810, 1993). However, this drug has showed limited success in producing cognitive improvement in **Alzheimer**'s disease patients and initially had major side effects such as liver toxicity. The second more recently FDA approved drug, donepezil ("Aricept"), which is also an acetylcholinesterase inhibitor, is more effective tham tacrine, by demonstrating slight cognitive improvement in **Alzheimer**'s disease patients (Barner and (Gray, Ann. Pharmacotherapy 32:70-77, 1998; Rogers and Friedhoff, Eur. Neuropsych. 8:67-75, 1998), but is not believed to be a cure. Therefore, it is clear that there is a need for more effective treatments for **Alzheimer**'s disease patients.

SUMM [0013] Amyloid as a Therapeutic Target for **Alzheimer**'s Disease

SUMM [0014] **Alzheimer**'s disease is characterized by the deposition and accumulation of a 39-43 amino acid peptide termed the beta-amyloid protein, A.beta. or. . .

SUMM . . . A.beta. peptide is a major component which makes up the amyloid deposits of "plaques" in the brains of patients with **Alzheimer**'s disease. In addition, **Alzheimer**'s disease is characterized by the presence of numerous neurofibrillary "tangles", consisting of paired helical filaments which abnormally accumulate in the. . . Kosik et al., Proc. Natl. Acad. Sci. USA 83:4044-4048, 1986; Lee et al., Science 251:675-678, 1991). The pathological hallmark of **Alzheimer**'s disease is therefore the presence of "plaques" and "tangles", with amyloid being deposited in the central core of the plaques. The other major type of lesion found in the **Alzheimer**'s disease brain is the accumulation of amyloid in the walls of blood vessels, both within the brain parenchyma and in. . .

SUMM [0016] For many years there has been an ongoing scientific debate as to the importance of "amyloid" in **Alzheimer**'s disease, and whether the "plaques" and "tangles" characteristic of this disease were a cause or merely a consequence of the disease. Within the last few years, studies now indicate that amyloid is indeed a causative factor for **Alzheimer**'s disease and should not be regarded as merely an innocent bystander. The **Alzheimer**'s A.beta. protein in cell culture has been shown to cause degeneration of nerve cells within short periods of time (Pike. . . cell death in transgenic mice (Games et al., Nature 373:523-527, 1995; Hsiao et al., Science 274:99-102, 1996). Injection of the **Alzheimer**'s A.beta. into rat brain also causes memory impairment and neuronal dysfunction (Flood et al., Proc. Natl. Acad. Sci. USA 88:3363-3366,. . .

SUMM [0017] Probably, the most convincing evidence that A.beta. amyloid is directly involved in the pathogenesis of **Alzheimer**'s disease comes from genetic studies. It has been discovered that the production of A.beta. can result from mutations in the. . . Nature Med. 1: 1291-1296, 1995). The identification of mutations in the beta-amyloid precursor protein gene which causes early onset familial **Alzheimer**'s disease is the strongest argument that amyloid is central to the pathogenetic process underlying this disease. Four reported disease-causing mutations have now been discovered which demonstrate the importance of A.beta. in causing familial **Alzheimer**'s disease (reviewed in Hardy, Nature Genet. 1:233-234, 1992). All of these studies suggest that providing a drug to reduce, eliminate. . .

SUMM . . . identification of new compounds or agents as potential therapeutic agents to arrest amyloid deposition, accumulation and/or persistence that occurs in **Alzheimer**'s disease and other

amyloidoses are desperately sought.

SUMM [0020] Parkinson's disease is a **neurodegenerative** disorder that is pathologically characterized by the presence of intracytoplasmic Lewy bodies (Lewy in Handbuch der Neurologie, M. Lewandowski, ed.,. . . nucleation-dependent polymerization process (Wood et al., J. Biol. Chem. 274:19509-19512, 1999). In this regard .alpha.-synuclein fibril formation resembles that of **Alzheimer**'s beta-amyloid protein (A.beta.) fibrils. .alpha.-Synuclein recombinant protein, and non-amyloid component (known as NAC-P), which is a 35-amino acid peptide fragment. . .

SUMM [0021] Parkinson's disease .alpha.-synuclein fibrils, like the A.beta. fibrils of **Alzheimer**'s disease, also consist of a predominant beta-pleated sheet structure. We believe, therefore, that compounds found to inhibit **Alzheimer**'s disease A.beta. amyloid fibril formation can also be anticipated to be effective in the inhibition of .alpha.-synuclein fibril formation. These compounds would therefore also serve as therapeutics for Parkinson's disease, in addition to having efficacy as a therapeutic for **Alzheimer**'s disease and other amyloid disorders.

SUMM . . . one such compound is administered; the mammal is a human; and the amyloidosis is selected from the group consisting of **Alzheimer**'s disease, Down's syndrome, hereditary cerebral hemorrhage with amyloidosis of the Dutch type, the amyloidosis of chronic inflammation, the amyloidosis of. . . with carpal tunnel syndrome, senile cardiac amyloidosis, familial amyloidotic polyneuropathy, and the amyloidosis associated with endocrine tumors, and especially is **Alzheimer**'s disease.

SUMM . . . contains only one such compound, the mammal is a human; and the amyloidosis is selected from the group consisting of **Alzheimer** 's disease, Down's syndrome, hereditary cerebral hemorrhage with amyloidosis of the Dutch type, the amyloidosis of chronic inflammation, the amyloidosis of. . . with carpal tunnel syndrome, senile cardiac amyloidosis, familial amyloidotic polyneuropathy, and the amyloidosis associated with endocrine tumors, and especially is **Alzheimer** 's disease.

SUMM . . . Assay 1 below, while their activity in vivo against amyloidoses can be measured in animal models, such as those of **Alzheimer**'s disease and in humans by a method such as that discussed in Assay 2 below.

SUMM . . . accompanied by a label indicating the intended method of treatment, such as the treatment of an amyloid disease, such as **Alzheimer**'s disease, or of a disease associated with .alpha.-synuclein fibril formation, such as Parkinson's disease. A "therapeutically effective dosage" preferably inhibits. . .

DETD [0105] Disassembly/Disruption of **Alzheimer**'s Disease A.beta. 1-42 Fibrils by Polyhydroxylated Aromatic Compounds

DETD . . . compounds which consist of various polyhydroxylated aromatic containing structures were tested for their ability to cause a disassembly/disruption of pre-formed **Alzheimer**'s disease amyloid fibrils containing A.beta. 1-42. This type of activity would be important for any potential anti-amyloid drug which can be used in patients who already have substantial amyloid deposition in organs and/or tissues. For example, **Alzheimer**'s disease patients in mid-to-late stage disease have abundant A.beta.-containing amyloid deposits in their brains as part of both **neuritic** plaques and cerebrovascular amyloid deposits. A compound capable of causing disassembly/disruption of pre-existing amyloid deposits would be advantageous for use. . .

DETD . . . and K. Nakakuki, Lab. Invest. 74:374-383, 1996) was employed to identify potential therapeutic compounds capable of causing a disassembly/disruption of **Alzheimer**'s A.beta. 1-42 amyloid fibrils. Thioflavin T is known to bind to fibrillar amyloid proteins, and an increase in fluorescence correlates. . . fibril formation, whereas a decrease in fluorescence correlates with a decrease in amyloid fibril due to disassembly and/or disruption. The **Alzheimer**'s A.beta. protein (1-42) when placed in solution, such as distilled water, tends to spontaneously form amyloid fibrils. Using this sensitive. . . fibrils (see the documents cited above), allowing one to identify and quantitate the extent of potential inhibitors and/or enhancers of **Alzheimer**'s A.beta. 1-42 amyloid fibrils.

DETD . . . except that for quinic acid at the 2:1 ratio (asterisked in Table 1), which was not significant.

TABLE 1

Disassembly/disruption of **Alzheimer**`s 1-42 fibrils,
as indicated by Thioflavin T fluorescence inhibition

	Fluorescence inhibition, %, at the A.beta. 1-42: compound w/w ratios given

. . .

DETD [0114] Dose-Dependent Disassembly/Disruption of **Alzheimer**'s Disease A.beta. 1-40 Fibrils by Tannic Acid and Gallic Aid

DETD . . . acid at the 4:1 ratio (asterisked in Table 2), which was significant at the p<0.05 level.

TABLE 2

Dose-dependent disassembly/disruption of **Alzheimer**`s 1-40 fibrils,
as indicated by Thioflavin T fluorescence inhibition

Compound name. . .	Fuorescence inhibition, %, at the A.beta. 1-40: compound w/w ratios given

DETD [0117] Disaggregation of **Alzheimer**'s Disease A.beta. 1-40 Fibrils by Polyhydroxylated Aromatic Compounds

DETD . . . (asterisked in Table 3) at the p<0.05 level, and quinic acid (double asterisked), which was not significant.

TABLE 3

Disaggregation of **Alzheimer**`s 1-40 fibrils,
as indicated by Congo red spectrophotometry

Compound name	Decrease in absorbance, %
Gallic acid	52 .+-. 0.4
Ethyl gallate. . .	

DETD [0122] Dose-Dependent Disaggregation of **Alzheimer**'s Disease A.beta. 1-40 Fibrils by Tannic Acid and Gallic Acid

DETD . . . acid at the 4:1 ratio (asterisked in Table 4), which was significant at the p<0.05 level.

TABLE 4

Dose-dependent disaggregation of **Alzheimer**`s 1-40 fibrils,
as indicated by Congo red spectrophotometry

Decrease in absorbance, %,
at the A.beta. 1-42: compound
w/w ratios given

Compound name. . .

DETD . . . in vitro and in vivo assays may be used to test the compounds for their effectiveness in the treatment of **Alzheimer**'s disease, such as those described in European Published Patent Application No. 0 659 418.

DETD . . . have ceased menstruating for between 6 and 12 months prior to the study's initiation, have been diagnosed with early stage **Alzheimer**'s disease (AD), are expected to have worsening symptoms of AD within the study period, but are in good general health. . .

CLM What is claimed is:

4. The method of claim 3 where the amyloidosis is selected from the group of diseases consisting of **Alzheimer**'s disease, Down's syndrome, hereditary cerebral hemorrhage with amyloidosis of the Dutch type, the amyloidosis of chronic inflammation, the amyloidosis of. . .

5. The method of claim 4 where the amyloidosis is **Alzheimer**'s disease.

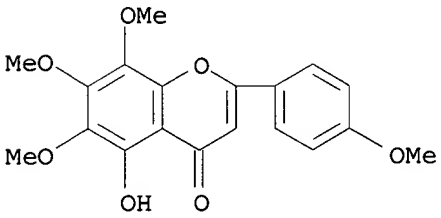
8. The drug product of claim 7 indicated for the treatment of **Alzheimer**'s disease.

IT 51-61-6, Dopamine, biological studies 59-92-7, Dopa, biological studies 72-48-0, Alizarin 77-95-2, Quinic acid 81-61-8, Quinalizarin 82-12-2, Rufigallol 82-83-7, Puberulonic acid 83-85-2, Fuscin 87-88-7, Chloranilic acid 90-18-6, Quercetagetin 90-19-7, Rhamnetin 99-11-6, Citrazinic acid 99-23-0, Puberulic acid 117-12-4, Anthrarufin 117-39-5, Quercetin 118-76-3, Rhodizonic acid 121-79-9, Propyl gallate 128-68-7, Phenicin 148-25-4, Chromotropic acid 149-45-1, Tiron 149-91-7, Gallic acid, biological studies 152-84-1, Ruberythric acid 153-18-4, Rutin 154-23-4, Catechin 301-19-9, Robinin 305-01-1, Esculetin 319-89-1, Tetroquinone 437-50-3, Gentisin 446-72-0, Genistein 475-25-2, Hematein 475-54-7, Oosporein 478-43-3, Rhein 478-60-4, Citromycetin 480-15-9, Datiscetin 480-16-0, Morin 480-17-1, Leucocyanidin 480-40-0, Chrysin 480-44-4, Acacetin 481-74-3, Chrysophanic acid 484-89-9, Fumigatin 486-35-1, Daphnetin 489-32-7, Icariin 490-46-0, Epicatechin 491-45-2, Phloroglucide 491-50-9, Quercimeritrin 491-58-7, Chrysarobin 491-67-8, Baicalein 491-70-3, Luteolin 497-75-6, Dioxethedrine 499-14-9, Chondrosine 501-15-5, Deoxyepinephrine 517-82-8, Echinochrome a 517-88-4, Alkannin 517-92-0, Chrysamminic acid 518-82-1, Emodin 519-34-6, Maclurin 520-18-3, Kaempferol 520-27-4, Diosmin 520-34-3, Diosmetin 520-36-5, Apigenin 524-30-1, Fraxin 528-21-2, Gallacetophenone 528-48-3, Fisetin 528-50-7, Cellobiose 528-53-0, Delphinidin 528-58-5, Cyanidin 529-53-3, Scutellarein 531-58-8, Cichoriin 533-73-3, 1,2,4-Benzenetriol 536-08-3, Digallic acid 548-80-1, Chromotrope 2B 548-83-4, Galangin 550-24-3, Embelin 552-21-6, Methylenedigallic acid 552-58-9, Eriodictyol 568-02-5, Alizarin blue 568-93-4, Alizarin orange 569-77-7, Purpurogallin 574-84-5, Fraxetin 577-33-3, Anthrarobin 578-74-5, Apigetrin 602-64-2, Anthragallol 602-92-6, Dibromogallic acid 618-73-5, Gallamide 831-61-8, Ethyl gallate 970-73-0, Gallocatechin 970-74-1, Epigallocatechin 1143-38-0, Anthralin 1260-17-9, Carminic acid 1397-77-9, Actinorhodine 1403-56-1, Fomecin a 1404-52-0, Rhodomycin b 1471-96-1, Echinochrome a 1562-85-2, Gallocyanine 1702-77-8, Fusarubin 1927-04-4, 5-Hydroxydopamine 2103-64-2, Gallein

2611-67-8, Cyanidin 3,5-diglucoside **2798-20-1**, Gardenin b
3101-51-7, Ergoflavin 4589-33-7, Bostrycoidin 5908-63-4, Baptigenin
7084-24-4, Cyanidin 3-glucoside **7085-55-4**, Troxerutin
10140-70-2, Curvularin 13405-60-2, .beta. Glucogallin 15979-35-8,
Laccaic acid a 16545-11-2, Guamecycline 16790-41-3, Fomecin b
17249-00-2, Laccaic acid b 18376-31-3, Cyanidin 3-sophoroside
18499-84-8, Laccaic acid d 18499-92-8, Kermesic acid 18719-76-1,
Cyanidin 3-rhamnoglucoside 19879-06-2, Granaticin 20004-62-0,
Resistomycin 20725-03-5, Fustin 20830-81-3, Daunorubicin
21187-73-5, Gardenin a 21637-25-2, Isoquercitrin 23214-92-8,
Doxorubicin 23241-56-7, Laccaic acid c 23444-65-7, Alkannin
23651-95-8, Droxidopa 23666-50-4, Rhodomycin a 27267-69-2,
Collinomycin 27613-78-1, Alizarinsulfonic acid 28860-95-9, Carbidopa
29202-00-4, Gardenin d **29550-05-8**, Gardenin c
29550-07-0, Gardenin e 35595-03-0, Centaurein 36413-60-2,
Quinic acid 38820-68-7, Cyanidin 3-sophoroside 42927-70-8, Apiose
50935-04-1, Carubicin 52479-85-3, Exifone 53318-36-8, .alpha.
Glucogallin 67227-56-9, Fenoldopam 71628-96-1, Menogaril
75775-33-6, Purpurin 80455-68-1, Fredericamycin a 97689-87-7,
Tunichrome B1 349584-11-8
(polyhydroxylated arom. compds. for the treatment of amyloidosis and .alpha.-synuclein fibril diseases)

IT **2798-20-1**, Gardenin b **7085-55-4**, Troxerutin
21187-73-5, Gardenin a **29202-00-4**, Gardenin d
29550-05-8, Gardenin c **29550-07-0**, Gardenin e
(polyhydroxylated arom. compds. for the treatment of amyloidosis and .alpha.-synuclein fibril diseases)

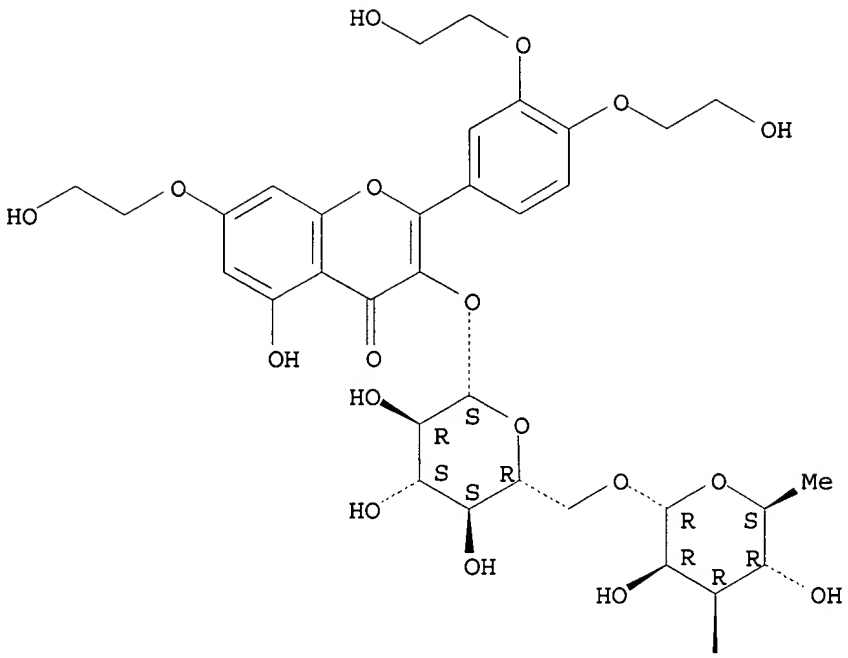
RN 2798-20-1 USPATFULL
CN 4H-1-Benzopyran-4-one, 5-hydroxy-6,7,8-trimethoxy-2-(4-methoxyphenyl)- (9CI) (CA INDEX NAME)



RN 7085-55-4 USPATFULL
CN 4H-1-Benzopyran-4-one, 2-[3,4-bis(2-hydroxyethoxy)phenyl]-3-[[6-O-(6-deoxy-.alpha.-L-mannopyranosyl)-.beta.-D-glucopyranosyl]oxy]-5-hydroxy-7-(2-hydroxyethoxy)- (9CI) (CA INDEX NAME)

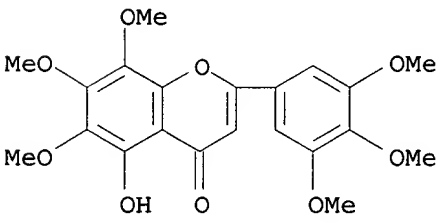
Absolute stereochemistry.

PAGE 1-A

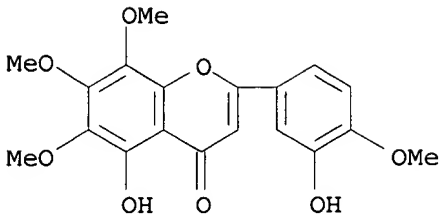


PAGE 2-A

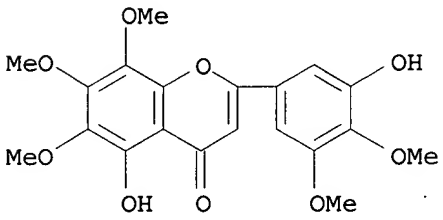
RN 21187-73-5 USPATFULL
CN 4H-1-Benzopyran-4-one, 5-hydroxy-6,7,8-trimethoxy-2-(3,4,5-trimethoxyphenyl)- (9CI) (CA INDEX NAME)



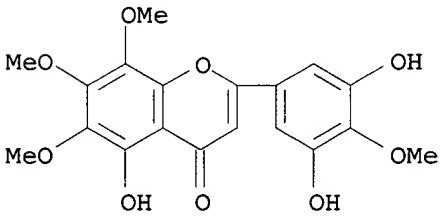
RN 29202-00-4 USPATFULL
CN 4H-1-Benzopyran-4-one, 5-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-6,7,8-trimethoxy- (9CI) (CA INDEX NAME)



RN 29550-05-8 USPATFULL
CN 4H-1-Benzopyran-4-one, 5-hydroxy-2-(3-hydroxy-4,5-dimethoxyphenyl)-6,7,8-trimethoxy- (9CI) (CA INDEX NAME)



RN 29550-07-0 USPATFULL
CN 4H-1-Benzopyran-4-one, 2-(3,5-dihydroxy-4-methoxyphenyl)-5-hydroxy-6,7,8-trimethoxy- (9CI) (CA INDEX NAME)



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